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# CONTENT OF PLATINUM AND PALLADIUM IN RAT TISSUES

## Correlation of Tissue Concentrations of Platinum and Palladium with Biochemical Effects

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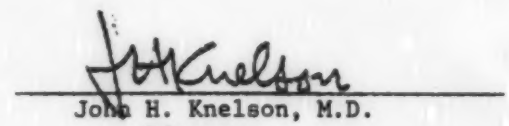
## FOREWORD

The many benefits of our modern, developing, industrial society are accompanied by certain hazards. Careful assessment of the relative risk of existing and new man-made environmental hazards is necessary for the establishment of sound regulatory policy. These regulations serve to enhance the quality of our environment in order to promote the public health and welfare and the productive capacity of our Nation's population.

The Health Effects Research Laboratory, Research Triangle Park, conducts a coordinated environmental health research program in toxicology, epidemiology, and clinical studies using human volunteer subjects. These studies address problems in air pollution, non-ionizing radiation, environmental carcinogenesis and the toxicology of pesticides as well as other chemical pollutants. The Laboratory develops and revises air quality criteria documents on pollutants for which national ambient air quality standards exist or are proposed, provides the data for registration of new pesticides or proposed suspension of those already in use, conducts research on hazardous and toxic materials, and is preparing the health basis for non-ionizing radiation standards. Direct support to the regulatory function of the Agency is provided in the form of expert testimony and preparation of affidavits as well as expert advice to the Administrator to assure the adequacy of health care and surveillance of persons having suffered imminent and substantial endangerment of their health.

This study provides a correlation between platinum and palladium levels in tissues and their biochemical effects. The information obtained from this study is important to the Catalyst Research Program in that it helps establish dose-response relationships for platinum and palladium salts in animals.



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## ABSTRACT

Data have been compiled on the platinum and palladium content in six rat tissues after the dietary administration of platinum or palladium salts. The platinum and palladium content in rat tissues does not appear to correlate with the rates of weight gain of rats, the organ weights, or the four parameters of drug metabolism which were studied.

This report was submitted in fulfillment of Order Number DA-6-99-6142J, Contract Number Z804557-01, by the University of North Carolina (at Chapel Hill) under the sponsorship of the Environmental Protection Agency. Work was completed as of July 1977.

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## SECTION 1

## INTRODUCTION

Platinum and palladium are used as the active components in the catalytic converters of air pollution control devices of motor vehicles. The use of these metals is accompanied by the potential loss of platinum and palladium into the environment. This laboratory has been involved in studies on the biochemical effects of these metals.[1-5]

## SECTION 2

## MATERIALS AND METHODS

### ANIMALS

Male Sprague-Dawley rats, obtained from Zivic-Miller Laboratories, were used in all experiments. The mean body weights were 100-110 g (4-5 weeks of age) when the rats were started on the diets.

The dietary administration ad libitum of metallic salts was conducted for 1 week (7.5 - 8.5 days), 4 weeks (28.5 - 32.5 days), or 13 weeks (87 - 93 days). The rats were housed four rats per cage. Body weights of individual rats and consumption of feed and water per cage were measured every seventh day. The metallic salts were administered either in the drinking water or by mixing in the dry feed (Purina Laboratory Chow).

The dietary levels and total consumption of platinum (Pt) and palladium (Pd) salts are given in Table 1.

### METAL ANALYSES ON TISSUE SAMPLES

Fresh tissue samples were weighed and frozen until analyses. Analyses for platinum or palladium were conducted by Stewart Laboratories.[6] The content of platinum or palladium is reported as micrograms (µg) of metal per gram (wet weight) of tissue.

The tissue samples were collected during earlier studies in this laboratory[1-5] on the biochemical effects of platinum and palladium. Data other than the metal analyses were reported in previous reports to the Environmental Protection Agency.[4,5]

TABLE 1. DIETARY LEVELS AND TOTAL CONSUMPTION OF PLATINUM AND PALLADIUM SALTS

| Group number | Metallic salt | Diet duration (weeks) | Dietary level[a] | Total consumption during diet period (mg Pt or Pd/rat) |
|---|---|---|---|---|
| 19 | $PtCl_4$ | 1 | 319 mg/liter (1.63) | 59 |
| 26 | $PtCl_4$ | 4 | 319 mg/liter (1.63) | 255 |
| 87 | $PtCl_4$ | 4 | 1147 mg/kg (5.88) | 743 |
| 105 | $PtCl_4$ | 4 | 2581 mg/kg (13.2) | 1616 |
| 53 | $PtCl_4$ | 13 | 106 mg/liter (0.54) | 389 |
| 17 | $Pt(SO_4)_2 \cdot 4H_2O$ | 1 | 106 mg/liter (0.54) | 26 |
| 25 | $Pt(SO_4)_2 \cdot 4H_2O$ | 1 | 319 mg/liter (1.63) | 78 |
| 85 | $Pt(SO_4)_2 \cdot 4H_2O$ | 4 | 1147 mg/kg (5.88) | 716 |
| 101 | $PtO_2$ | 4 | 5808 mg/kg (29.8) | 4308 |
| 75 | $PdCl_2$ | 4 | 1407 mg/kg (13.2) | 873 |
| 81 | $PdCl_2$ | 4 | 3166 mg/kg (29.8) | 2020 |
| 30 | $PdCl_2 \cdot 2H_2O$ | 1 | (satd. soln.) | -- |
| 77 | $PdSO_4$ | 4 | 625 mg/kg (5.88) | 407 |
| 103 | $PdSO_4$ | 4 | 3164 mg/kg (29.7) | 1868 |
| 97 | PdO | 4 | 3166 mg/kg (29.8) | 2276 |

[a]Dietary level is expressed as mg Pt or Pd/kg feed or as mg Pt or Pd/liter drinking water. Values in parentheses are mmoles/kg or mmoles/liter.

## SECTION 3

## RESULTS

### PLATINUM CONTENT IN RAT TISSUES

The platinum content in various tissues after dietary administration is given in Table 2.

After the dietary administration of any of the platinum salts, the metal contents in the tissues were in the following order: kidney > liver, spleen > blood, testis > brain. After four weeks on platinum-containing diets, the platinum content in the kidney generally was about 8-fold greater than the liver and spleen, and at least 16-fold greater than in the blood and testis, except when the highest dose of platinum was administered (group 105), and the content in the kidney was 3.5 to 5-fold greater than in the liver and spleen.

The dietary administration of platinum tetrachloride ($PtCl_4$) at 319 mg Pt/liter for one week resulted in low levels of platinum in the tissues. The continuation of the same diet for 4 weeks increased the total platinum intake by 4.3-fold and the platinum content in kidney, spleen and blood by at least 7-fold.

When the $PtCl_4$ was placed in the dry feed, and the platinum consumption during 4 weeks was increased greater than 2-fold (groups 87 versus 105, respectively), the platinum content in kidney showed no increase, but the contents in liver and spleen increased at least 2-fold.

The platinum content in the tissues was not appreciably different, although it was administered in the form of two different very water-soluble salts, $PtCl_4$ and platinum disulfate ($Pt(SO_4)_2$) (namely, groups 19 versus 25, and groups 85 versus 87).

TABLE 2. PLATINUM CONTENT IN RAT TISSUES AFTER ORAL ADMINISTRATION OF PLATINUM SALTS

| Group | Salt | Platinum Content (µg/gram wet weight; mean ± SE)[e] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Liver | Kidney | Spleen | Testis | Brain | Blood |
| 19 | $PtCl_4$ | 2.2 | 4.8 ±0.2 | 0.24 | -- | -- | 0.23 |
| 26 | $PtCl_4$ | 2.5 ±0.9 | 33.7 ±3.5 | 4.8 ±1.5 | 1.5 ±0.5 | 0.11 ±0.07 | 2.1 ±0.4 |
| 87 | $PtCl_4$ | 3.2 ±0.9 | 33.5 ±6.3 | 3.1 ±0.9 | 1.1 ±0.4 | <0.02 | 1.5 ±0.4 |
| 105[a] | $PtCl_4$ | 8.9 ±1.2 | 32.4 ±4.6 | 6.4 ±3.0 | 1.7 ±0.3 | 0.12 ±0.08 | 1.6 ±0.2 |
| 53[b] | $PtCl_4$ | 1.3 ±0.3 | 14.9 ±0.4 | 1.6 ±0.3 | 0.94 ±0.20 | <0.06 | 0.90 ±0.08 |
| 17[c] | $Pt(SO_4)_2 \cdot 4H_2O$ | 0.07 | 0.26 ±0.02 | <0.02 | <0.04 | -- | 0.05 |
| 25[d] | $Pt(SO_4)_2 \cdot 4H_2O$ | 0.85 | 4.6 | 0.13 | -- | <0.02 | 0.22 |
| 85 | $Pt(SO_4)_2 \cdot 4H_2O$ | 3.5 ±0.4 | 43.4 ±8.3 | 3.2 ±0.5 | 1.1 ±0.1 | 0.33 ±0.18 | 1.6 ±0.3 |
| 101 | $PtO_2$ | <2.2 | <2.2 | <0.02 | <0.07 | <0.02 | <0.04 |

[a] Heart, 2.4
[b] Heart, 0.20 ± 0.09
[c] Heart, <0.02
[d] Heart, 0.25
[e] SE is given for four values; only the mean is given when two values are available

When platinum dioxide ($PtO_2$) was administered in the diet, only small quantities of the platinum of this water-insoluble salt were found in any of the tissues even when the salt was administered at a very high level in the diet (group 101).

EFFECTS OF PLATINUM SALTS ON PARAMETERS OF DRUG METABOLISM

Effects of the dietary administration of platinum and palladium salts on parameters of drug metabolism have been reported previously by this laboratory.[1] All four parameters (activities of aniline hydroxylase and aminopyrine demethylase and the contents of cytochrome P-450 and cytochrome $b_5$) were expressed "per mg microsomal protein."

The platinum content in liver shows little correlation with the parameters of drug metabolism. The highest platinum content in liver, 9 µg Pt/g tissue, was observed in group 105 ($PtCl_4$, 2581 mg Pt/kg feed for 4 weeks). In this group the cytochrome P-450 content and the activity of microsomal aniline hydroxylase were normal and the activity of microsomal aminopyrine demethylase and the content of cytochrome $b_5$ were both increased. After 4-week diets of the soluble platinum salts, intermediate levels of platinum (2.5 - 3.5 µg Pt/g tissue) were found in groups 26, 85 and 87. All of the measured parameters of drug metabolism in liver were within normal limits. The administration of $PtCl_4$ for 13 weeks (group 53) resulted in a low level of tissue platinum (1.3 µg Pt/g tissue), normal levels of cytochromes P-450 and $b_5$, and increased levels of aniline hydroxylase and aminopyrine demethylase. The only group to show a reduced drug metabolism--reduced aniline hydroxylase--contained less than 1 µg Pt/g tissue; these animals showed reduced weight gain and the reduced drug metabolism may have been due to reduced feeding in group 25.

Correlation of Weight Gains by Rats and Tissue Level of Platinum

The weight gain by rats receiving $PtCl_4$ at a level of 319 mg Pt/liter

in drinking water (comparable to groups 19 and 26) showed reduced weight gain during the first week ($p < 0.01$) and a normal rate of weight gain during the second, third and fourth weeks on the diet. During the latter three weeks, the platinum content in kidney, spleen and blood were increasing at least 7-fold but the liver content was not appreciably changed. Likewise, rats receiving an equal molar level of $Pt(SO_4)_2 \cdot 4H_2O$ (group 25) showed a reduced weight gain during the first week which was comparable to that observed in the $PtCl_4$-treated rats during the first week. Rats treated with $PtCl_4$ at a level of 2581 mg Pt/kg feed showed markedly reduced weight gains during the first two weeks on the diet and a total weight gain during the four weeks of approximately two-thirds of the control animals.

Correlation of Tissue Weights of Rats and Tissue Level of Platinum

After adjustment of organ weights of platinum-treated rats for the observed body weight, treatment with platinum salts at the levels given in Table 1 did not alter the weights of any of the organs studied: liver, kidney, spleen, heart or testis. The lack of effect was observed in kidney even though the content was 30-45 µg Pt/g wet tissue.

Correlation of DNA, RNA and Protein Content and Tissue Level of Platinum

The contents of DNA, RNA and protein were determined in liver, kidney and spleen of two groups of platinum-treated rats and their corresponding controls. The dietary administration of $PtCl_4$ (2580 mg Pt/kg feed) (group 105) or $Pt(SO_4)_2 \cdot 4H_2O$ (1147 mg Pt/kg feed) (group 85) did not alter the tissue content of DNA (µmoles DNA-nucleotide/g wet tissue), RNA (µmoles RNA-nucleotide/g wet tissue) or protein (mg protein/g wet tissue) in any of the three tissues examined (liver, kidney or spleen). Thus, the levels of platinum attained in these tissues (Table 2) did not alter the content of these macromolecules.

Palladium Content in Rat Tissues after Dietary Administration

The palladium contents in various tissues after dietary administration are given in Table 3.

After the dietary administration of either of the slightly water-soluble palladium salts, namely $PdCl_2$ and $PdSO_4$, the metal contents in the tissues were in the following order: kidney > liver > spleen > testis > blood and brain. After 4 weeks on the palladium-containing diets, the Pd content in the kidney was at least 7-fold greater than in the liver and at least 18-fold greater than in the spleen.

The 4-week administration of very high and equal levels of $PdCl_2$ and $PdSO_4$ resulted in comparable levels of palladium in the tissues of the two groups (namely, groups 81 versus 103). In contrast, the administration of the water-insoluble PdO salt at a very high level resulted in only a trace amount of palladium in the kidney and generally nonmeasurable levels in the other tissues.

Effects of Palladium Salts on Parameters of Drug Metabolism

The highest level of hepatic palladium was observed in group 103 ($PdSO_4$, 3164 mg Pd/kg feed, 4 weeks) but animals in this group showed no alteration in drug metabolism. In two groups of rats treated with $PdCl_2$ (group 75 and a similarly treated group), all four parameters of drug metabolism exhibited appreciable increases. When the administered level of $PdCl_2$ was increased (group 81), the hepatic content of palladium was approximately the same (approximately 2 μg Pd/g tissue) but none of the parameters of drug metabolism were altered.

Two groups received a saturated solution of $PdCl_2 \cdot 2H_2O$ as the drinking water, similar to group 30. Both groups showed an appreciable reduction in aniline hydroxylase and in aminopyrine demethylase even though only a trace of palladium was found in the liver of rats in group 30 (Table 3) and these rats showed normal weight gain during the 4-week diet period. We do not have an explanation for the reduced drug metabolism in these rats.

TABLE 3. PALLADIUM CONTENT IN RAT TISSUES AFTER DIETARY ADMINISTRATION OF PALLADIUM SALTS

| Group | Salt | Palladium Content (µg/gram wet weight; mean ± SE)[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | Liver | Kidney | Spleen | Testis | Brain | Blood |
| 75 | $PdCl_2$ | 1.8 ±0.3 | 27.6 ±2.5 | 0.15 ±0.01 | 0.14 ±0.00 | <0.01 | <0.02 |
| 81 | $PdCl_2$ | 2.0 ±0.1 | 34.6 ±3.4 | 0.72 ±0.21 | 0.24 ±0.03 | <0.01 | <0.04 |
| 30 | $PdCl_2 \cdot 2H_2O$ | <0.08 | 0.50 ±0.07 | <0.01 | <0.01 | <0.01 | <0.01 |
| 77 | $PdSO_4$ | <0.03 | 0.08 ±0.01 | <0.02 | <0.01 | <0.01 | <0.01 |
| 103 | $PdSO_4$ | 3.2 ±0.6 | 21.9 ±3.1 | 0.94 ±0.17 | 0.26 ±0.07 | <0.01 | 0.16 ±0.06 |
| 97 | PdO | <0.02 | 0.15 ±0.02 | <0.01 | <0.01 | <0.01 | <0.01 |

[a]Mean ± SE for four values.

Correlation of Weight Gains by Rats and Tissue Levels of Palladium

The dietary administration of $PdCl_2$ or $PdSO_4$ at 3166 mg Pd/kg feed (groups 81 and 103, respectively) resulted in palladium levels in tissue (µg Pd/g wet tissue) of 22-35 in kidney, 2-3 in liver, 0.7-1.0 in spleen and 0.25 in testis (Table 3). The $PdCl_2$-treated rats (group 81) exhibited restricted weight gain during the first, second and third weeks. The total weight gain at the end of 4 weeks was three-fourths of that observed in controls. In the $PdSO_4$-treated rats (group 103), the total weight gain at the end of 4 weeks was one-half of that of controls.

Correlation of Tissue Weights of Rats and Tissue Level of Palladium

The dietary administration of $PdCl_2$ or $PdSO_4$ at the levels given in Table 1 and resulting in the tissue levels of palladium given in Table 3 did not alter consistently the tissue weights of liver, kidney, spleen, heart or testis when adjusted for the body weight. A small decrease in liver and kidney weights were observed in rats treated with $PdCl_2$ at 1407 mg/kg feed (group 75); however, no decrease was observed at a higher dietary level of $PdCl_2$ (3166 mg/kg feed) (group 81).

## SECTION 4

## DISCUSSION

The dietary administration of $PtCl_4$ in the drinking water at 0.54 millimoles/liter for 13 weeks (group 53 of Table 1) resulted in the accumulation of platinum in the kidney to 76 nanomoles/g wet tissue. The kidneys were not enlarged significantly in these animals. Likewise, the dietary administration of $Pd^{2+}$ salts does not result in kidney enlargement. In an earlier study, the dietary administration of $PbCl_2$ in the drinking water at 3.7 millimoles/liter for 13 weeks resulted in the accumulation of lead in the kidney to 64 nanomoles/g wet tissue. In contrast with the results with platinum or palladium, however, the kidneys were approximately 25% larger ($p < 0.01$) in lead-treated rats than in the corresponding control animals.

The dietary administration of water-soluble salts of platinum--platinum tetrachloride and platinum disulfate tetrahydrate--results in a rate of weight gain less than in control rats for the first few weeks on the diet and is accompanied by some accumulation of platinum in the tissues. During later periods (e.g., third and fourth weeks) on the diet, the rate of weight gain (g/week/rat) by platinum-treated rats is equal to that of control animals even when the accumulation of platinum in the tissues is increasing. Such a finding is consistent with the proposal that the synthesis of a platinum-binding protein is induced during the first week of dietary administration. The binding of platinum to the metal-binding protein during the latter weeks may sequester the platinum and prevent the manifestation of its toxicity.

The proposal is made here (see also reference 1) that there is an inducible metal-binding protein for platinum and palladium, by analogy with the findings for other toxic metals. Such metal-binding proteins have been found for $Cd^{2+}$, $Zn^{2+}$ and $Hg^{2+}$ (i.e., metallothionein) and for $Cu^{2+}$ (i.e.,

copper-chelatin). These metal-binding proteins contain 25-33 mole percent cysteine, and $Pt^{4+}$ and $Pd^{2+}$ may bind to the same or similar proteins. The following indirect evidence is consistent with the existence of metal-binding protein(s) for $Pt^{4+}$ and/or $Pd^{2+}$. (a) The prior injection of a low level of platinum salt before the injection of a normally lethal dose of platinum salt protects against the acute lethality of the latter treatment.[1] (b) Although rats on $Pt^{4+}$- or $Pd^{2+}$-containing diets often show reduced weight gain during early dietary administration, the rate of weight gain often returns to normal after continuation of the diet for several weeks. (c) Although acute administration (and occasionally 1-week dietary administration) results in a decrease in xenobiotic metabolism, longer term dietary administration of $Pt^{4+}$ or $Pd^{2+}$ does not decrease the capabilities for xenobiotic metabolism.

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